PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Small volume plasma exchange for Guillain-Barré syndrome in resource-limited settings: a phase II safety and feasibility study
AUTHORS	Islam, Md Badrul; Islam, Zhahirul; Rahman, Shafiqur; Endtz, Hubert; Vos, Margreet; van der Jagt, Mathieu; Van Doorn, Peter; Jacobs, BC; Mohammad, Quazi

VERSION 1 – REVIEW

REVIEWER	David Cornblath Johns Hopkins University School of Medicine (Neurology), USA
REVIEW RETURNED	02-Apr-2018

GENERAL COMMENTS	This is an important paper as treatments for GBS remain unaffordable for much of the world's population. The authors have done a nice study of the safety and feasibility of SVPE in a small number of GBS patients. The main issue for me is a fuller discussion of the "dose" of plasma removed compared to standards currently in use. For example the 'dose' of PLEX is not stated in the introduction unlike the dose for IVIg. I think the authors should clearly state the doses of PLEX used in the pivotal studies (for example, 200-250 ml/kg in the North American study) and then clearly compare those to that used in this study which ended up as 140 ml/kg. Will the dose matter? This is important as it is not clear where the 8L volume target came from. Using the North American volume, the mean 60 kg person in this study would have received 12L of exchange in that study. Does this matter in the long run is critical. On page 17 lines 376-7, it is not clear what disease the authors refer to and how large that study was compared to the original NA and French studies. Possibly a Table comparing these would help.

REVIEWER	H WILLISON University of Glasgow, UK
REVIEW RETURNED	06-Apr-2018

GENERAL COMMENTS	The introduction and/or discussion would benefit from more textual content and referencing of SVPE studies and methods conducted elsewhere (e.g. PMID: 2246192), similarly a more detailed critique of other studies on comparison of modified PE techniques and ensuing economic benefits (e.g. PMID: 27605847).

	The principle presumptive effect of PE, including SVPE, is to remove pathogenic immunoglobulin, alongside other pro-inflammatory serum factors (e.g complement components), whilst maintaining sufficient vital serum factors (e.g. clotting factors and colloidal albumin). Normal human IVIg infusion is also a major recognised treatment for GBS. The choice of replacement fluid in this study was FFP, which contains both complement components and normal human IgG. As such, a) the introduction and discussion would benefit from a more critical analysis of the rationale for the choice of FFP (in contrast to other material e.g. saline and/or albumin) and b) the results section would have benefited from reporting data on the amount of FFP replacement in each patient (from which the total infused 'therapeutic' IVIg could be calculated), and reporting of serial serum IgG levels over the course of the treatment and post-treatment period. The autoantibodies responsible for causing GBS in Banglasdesh, at least following Campylobacter, are known. Reporting the serial autoantibody titres and CH50 activity would have been a useful addition to demonstrate effective clearance of putative neurotoxic factors by SVPE. Even though this is only intended a safety study, there is room to extract as much useful information as possible, provided it is not used to make unsubstantiable claims. In this report the authors have scrupulously avoided making any such claims, possibly at the expense of reportting the more detailed biomarker information referred to above.

VERSION 1 – AUTHOR RESPONSE

Response for Reviewer(s)' Comments to below:

Reviewer: 1

Reviewer Name: David Cornblath

Institution and Country: Johns Hopkins University School of Medicine (Neurology), USA

1. This is an important paper as treatments for GBS remain unaffordable for much of the world's population. The authors have done a nice study of the safety and feasibility of SVPE in a small number of GBS patients.

Response: *We thank the reviewer for his appreciation of our work.*

2. The main issue for me is a fuller discussion of the "dose" of plasma removed compared to standards currently in use. For example the 'dose' of PLEX is not stated in the introduction unlike the dose for IVIg. I think the authors should clearly state the doses of PLEX used in the pivotal studies (for example, 200-250 ml/kg in the North American study) and then clearly compare those to that used in this study, which ended up as 140 ml/kg. Will the dose matter?

Response: *Thanks for figuring out this issue. In the revised version we added the standard dose of plasma exchange in the introduction (Page 6, Line 112-116). Thereafter we discussed and compared*

our plasma exchange dose of 140 ml/kg with the current dose of PLEX (Page 17, Line 385-89).

3. This is important as it is not clear where the 8L volume target came from. Using the North American volume, the mean 60 kg person in this study would have received 12L of exchange in that study. Does this matter in the long run is critical.

Response: *Information from the existing literature based on the pivotal studies on plasma exchange indicates that the volume of patient plasma removal through plasma exchange for clinical benefit in an adult GBS patient should be at least six liter* (French Cooperative Group on Plasma Exchange in Guillain-Barré Syndrome. Appropriate number of plasma exchangesin Guillain-Barré Syndrome. Annals of Neurology 1997;41(3):298–306. PUBMED: 9066350). *From our previous pilot experience, we have observed that daily removal of 1000 ml of patient plasma is feasible through SVPE. Considering the safety of the procedure we designed to shorten the duration of SVPE (8 days) as well as targeted to remove substantial plasma volume that would benefit the patient. Eventually we came up with the feasible target plasma volume of 8 liters to be removed in eight days. This issue has been mentioned in the revised version of the manuscript (Page 17; Line 391-93)*

4. On page 17 lines 376-7, it is not clear what disease the authors refer to and how large that study was compared to the original NA and French studies. Possibly a Table comparing these would help.

Response: *We agree with the reviewer that the statements in the mentioned lines are less clear. We meant PLEX for Guillain-Barré syndrome and added reference from the large French study* (French Cooperative Group on Plasma Exchange in Guillain-Barré Syndrome. Appropriate number of plasma exchangesin Guillain-Barré Syndrome. Annals of Neurology 1997;41(3):298–306. PUBMED: 9066350) *in the revised version of the manuscript. (Page 17, Line 385-89)*

Reviewer: 2

Reviewer Name: H WILLISON

Institution and Country: University of Glasgow, UK

Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below

1. The introduction and/or discussion would benefit from more textual content and referencing of SVPE studies and methods conducted elsewhere (e.g. PMID: 2246192), similarly a more detailed critique of other studies on comparison of modified PE techniques and ensuing economic benefits (e.g. PMID: 27605847).

Response: *We acknowledge the reviewer's concern and addressed the other plasma removal methods conducted elsewhere along with the potential economic benefit of SVPE over those methods in the discussion (page 18; Line 417-26) section.*

2. The principle presumptive effect of PE, including SVPE, is to remove pathogenic immunoglobulin, alongside other pro-inflammatory serum factors (e.g complement components), whilst maintaining sufficient vital serum factors (e.g. clotting factors and colloidal albumin). Normal human IVIg infusion is also a major recognised treatment for GBS. The choice of replacement fluid in this study was FFP, which contains both complement components and normal human IgG. As such,

   a) The introduction and discussion would benefit from a more critical analysis of the rationale for the choice of FFP (in contrast to other material e.g. saline and/or albumin)

   Response: *As per the reviewer's suggestions we have mentioned the rational for the choice of FFP and critically analyzed the selection of FFP over other replacement fluids like human albumin or colloid solutions in the discussion section (Page 17-18; Line 398-415) of the resubmitted manuscript. It is important to mention that we also used normal saline as replacement fluid along with FFP as we have mentioned in our manuscript (Page 19; Line 408-409). Our main concern was patient safety as well as to reduce the cost of SVPE.*

   b) The results section would have benefited from reporting data on the amount of FFP replacement in each patient (from which the total infused 'therapeutic' IVIg could be calculated), and reporting of serial serum IgG levels over the course of the treatment and post-treatment period.

   The autoantibodies responsible for causing GBS in Banglasdesh, at least following Campylobacter, are known. Reporting the serial autoantibody titres and CH50 activity would have been a useful addition to demonstrate effective clearance of putative neurotoxic factors by SVPE.

   Even though this is only intended a safety study, there is room to extract as much useful information as possible, provided it is not used to make unsubstantiable claims. In this report the authors have scrupulously avoided making any such claims, possibly at the expense of reporting the more detailed biomarker information referred to above.

   Response: *According to the suggestion, we have included the amount of the FFP transfused to the 20 GBS patients in terms of median and range volume of FFP transfused. Furthermore the fraction of the traditional IVIg dose is also calculated from the amount of the FFP transfused to the patients and mentioned in the result section (Page 15-16; Line 353-57).*

   We admit that the CH50 activity of our patients and serial autoantibody titers over the

course of the SVPE treatment and post-treatment period was indeed quite informative. However in the original study design we didn't consider this mainly because our focus was safety of the patient and efficacy of the SVPE procedure. Also limitation of funding hindered us from looking into the antecedent infectious etiologies and serial serum auto-antibody titer levels. Certainly we do positively consider these measurements in the future SVPE trials focusing on the clinical efficacy.

VERSION 2 – REVIEW

REVIEWER	David Cornblath Johns Hopkins University, USA
REVIEW RETURNED	03-May-2018

GENERAL COMMENTS	Based on the additional data supplied by the authors, this trial is much more complicated than the title would imply. I raised the question of dose of PLEX and the other reviewer raised the question of amount of IgG in the FFP that was used as replacement. Both of these issues requires further exploration. The authors have suggested that the French trial of the appropriate number of exchanges in GBS concluded that 4 were as good as 6 in severe cases and that 4 were better than 2 in moderate cases. the question is 4 exchanges of what volume? The paper says the exchanges were each 1.5 plasma volumes but the exact volume is unclear to this reviewer after again reading the French paper. I think the authors concluded this was then 6 L but is 4 exchanges of 1.5 plasma volumes really 6L? Or is it something else? This would need to be clarified so that the volumes achieved by SVPE can be put in perspective with prior studies. The second important issue is the use of FFP which contains IgG. The authors report that their patients actually received almost 1 gm/kg of IgG. This may also be an important feature of the SVPE treatment regimen as dose responses studies in GBS are unknown. 2 gm/kg is standard and unchallenged. Thus is the intervention SVPE or PE/IVIg lite? Should this be clearer throughout the paper and title? Does this change the economics of the entire procedure?

REVIEWER	Hugh Willison University of Glasgow, UK
REVIEW RETURNED	02-May-2018

GENERAL COMMENTS	The authors have addressed my comments

VERSION 2 – AUTHOR RESPONSE

1. Response: We thank the reviewer for his comments.

Reviewer: 1
Reviewer Name: David Cornblath
Institution and Country: Johns Hopkins University, USA
Please state any competing interests or state 'None declared': none

Please leave your comments for the authors below

1. Based on the additional data supplied by the authors, this trial is much more complicated than the title would imply. I raised the question of dose of PLEX and the other reviewer raised the question of amount of IgG in the FFP that was used as replacement. Both of these issues requires further exploration.

The authors have suggested that the French trial of the appropriate number of exchanges in GBS concluded that 4 were as good as 6 in severe cases and that 4 were better than 2 in moderate cases. the question is 4 exchanges of what volume? The paper says the exchanges were each 1.5 plasma volumes but the exact volume is unclear to this reviewer after again reading the French paper. I think the authors concluded this was then 6 L but is 4 exchanges of 1.5 plasma volumes really 6L? Or is it something else? This would need to be clarified so that the volumes achieved by SVPE can be put in perspective with prior studies.

1. Response: We apologize for the unclarity about our initial description of the nature of the treatment and appreciate the reviewers concern. Indeed the French RCT indicated that one exchange was 1.5 plasma volume but the plasma volume may differ between patients and was not reported in detail.[1] Therefore the exact total plasma volume (in L) exchanged per patient during PE in this RCT remains unknown. However, it was also mentioned in this study that the rate of exchange per session was 40-ml/kg body weight. According to that a 60-70 kg person should have an exchange of 2400-2800 ml per session. A second RCT conducted by the same group targeted for a two plasma volume exchange per session (3.5 L) and 4 PE sessions were done for each patient in 8 days and removing 6 – 12 L plasma per patient.[2] Additionally an American RCT [3]on GBS showed beneficial effect of PE over conventional supportive therapy.[3] The exchange rate was 40-50 ml/kg/session, for 3 to 5 sessions in 7 to 14 days, which comes to a total PE volume of 120-250 ml/kg. In our study the median total PE volume exchanged during SVPE was 8.4 L with a rate of 140 ml/kg. Therefore, in our view the exchanged plasma volume in the SVPE study was within the same range as in both the French and American RCT on PE for adult GBS patients. We have specifically mentioned the plasma exchange volumes and rates in the second revision of the manuscript **(Page: 6, Line 113-14 and Page: 17, Line 385-396, 400-01)**

2. The second important issue is the use of FFP, which contains IgG. The authors report that their patients actually received almost 1 gm/kg of IgG. This may also be an important feature of the SVPE treatment regimen as dose responses studies in GBS are unknown. 2 gm/kg is standard and unchallenged.

Thus is the intervention SVPE or PE/IVIg lite? Should this be clearer throughout the paper and title? Does this change the economics of the entire procedure?

2. Response:

The reviewer raised an important aspect of the use of FFP as replacement fluid in SVPE. The volume of FFP transfused in SVPE nearly provided half the dose (1 g/kg) of traditional IVIg dose in GBS (2 g/kg). However, FFP was also used to replace half of the amount of plasma removed through PE in previous trials.[1 2] This comes with a volume of 6 L of FFP as replacement fluid in standard PE (removing 12 L plasma in 4 PE sessions), which is the same volume of FFP we used in SVPE.

We cannot exclude that the IgG transfused via FFP may have contributed to the therapeutic response nor can the other published plasma exchange studies. We have previously mentioned in the manuscript the potential effect of IgG present in FFP used as replacement fluid **(Page: 18, lines: 407-18)**. But in our view a large proportion of the transfused IgG is washed away during the SVPE sessions, as also occurred during standard PE and the remaining amount of IgG effect is probably considerably much lower. Therefore we prefer not to use the term 'PE/IVIg lite' in the title as in other studies evaluating PE in GBS that also used FFP as plasma replacement. This has been further emphasized in the manuscript **(Page: 18, lines: 424-25)**

The costs for using FFP as plasma replacement was already included in our estimated total costs for the SVPE treatment in Bangladesh (500 US$). In fact, FFP is much cheaper than other replacement fluids used during PE including human albumin or synthetic colloid solutions. To clarify this the cost of the full course of SVPE is mentioned in the new version of the manuscript **(Page: 9-10, lines: 205-08)**.

References

1. The French Cooperative Group on Plasma Exchange in Guillain-Barre Syndrome. Appropriate number of plasma exchanges in Guillain-Barre syndrome. *Ann Neurol* 1997;41(3):298-306.
2. French Cooperative Group on Plasma Exchange in Guillain-Barre syndrome. Efficiency of plasma exchange in Guillain-Barre syndrome: role of replacement fluids. *Ann Neurol* 1987;22(6):753-61.
3. The Guillain-Barre syndrome Study Group. Plasmapheresis and acute Guillain Barre syndrome. *Neurology* 1985; 35(8):1096-104.

VERSION 3 – REVIEW

REVIEWER	David Cornblath, MD Johns Hopkins University. USA
REVIEW RETURNED	29-May-2018

GENERAL COMMENTS	I remain concerned that the authors have not acknowledged that this procedure provides PE at the lower end of the pivotal studies (North American study used 150-250 ml/kg) and also IVIg exposure at 1 gm/kg. For the latter the authors claim that the infused IVIg is only there for 8-12 hours before SVPE is started but how can they know if this is important or not? Certainly the IVIg is not all taken away as they also imply. Is the 8-12 hours for external IVIg enough? No one can say. None of these lessen what the authors have done but rather may provide a more complete picture to explain the effect. Can this be added to Abstract as now hidden deep in paper?

VERSION 3 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: David Cornblath, MD
Institution and Country: Johns Hopkins University. USA
Please state any competing interests or state ‘None declared’: none

Please leave your comments for the authors below

I remain concerned that the authors have not acknowledged that this procedure provides PE at the lower end of the pivotal studies (North American study used 150-250 ml/kg) and also IVIg exposure at 1 gm/kg. For the latter the authors claim that the infused IVIg is only there for 8-12 hours before SVPE is started but how can they know if this is important or not? Certainly the IVIg is not all taken away as they also imply. Is the 8-12 hours for external IVIg enough? No one can say.

None of these lessen what the authors have done but rather may provide a more complete picture to explain the effect. Can this be added to Abstract as now hidden deep in paper?

Response: We agree with the reviewer that the amount of plasma exchanged in SVPE was at the lower end of the North American study where the exchange rate was150-250 ml/kg1. Now we have specified the volume exchanged in the abstract and mention this in the strength and limitations section adjacent to the abstract and discussion. (Page: 3, Line: 73-74; Page: 5, Line: 100-1 and Page: 17, Line: 400-2).

We also agree, we cannot exclude that the IVIg derived from the FFP we used as plasma replacement could have had a therapeutic effect, although the dosage was less than half of the standard IVIg treatment for GBS of which a substantial proportion was probably removed during SVPE sessions. We explain that the dosage of IgG that was admitted via FFP also in the new version of the abstract. (Page: 3, Line: 64; Page: 4, Line: 75-76 and Page: 18, Line: 433-35).

1. Plasmapheresis and acute Guillain-Barre syndrome. The Guillain-Barre syndrome Study Group. Neurology 1985;35(8):1096-104. [published Online First: 1985/08/01]

**Please follow the page and line numbers as per the clean copy of the revised manuscript.